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08/319,357 10/06/94 SCHMITT-WILLICH

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EXAMINER

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12M1/0919  
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ART UNIT PAPER NUMBER

37

DATE MAILED:

09/19/96

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

Responsive to communication(s) filed on 4-19-96, 4-29-96 + 7-1-96

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 2-9, 11, 13, 14, 16, 18-26, 29, 30, 32, 36-43 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 2-9, 11, 13, 14, 16, 18-26, 29, 30, 32, 36-43 is/are rejected.

Claim(s) \_\_\_\_\_ is/are objected to.

Claims \_\_\_\_\_ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) \_\_\_\_\_

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of Reference Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 19

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

1. Applicant's declarations filed 4/26/96 and 4/29/96 have been considered. The finality of the previous office action is withdrawn pursuant to 37 CFR 1.29(a).

The declaration submitted by Dr. Muhler demonstrates the unexpected results of the Gd-DTPA analogs containing a pendent alkoxybenzyl group over those Gd complexes with an alkoxyalkyl substituent. This experiment is found persuasive in overcoming the previous obviousness rejection over Berg in view of Gries.

The declaration submitted by Dr. Schumann-Giampieri has also been considered. The results of this second experiment compare the adjacent homologs of Gd-ethoxybenzyl DTPA and Gd-methoxybenzyl DTPA and demonstrate the unpredictability in the art which in turn demonstrates the unobviousness of the claimed methods over Meares et al. (U.S. Pat. No. 4,622,420). This reference was never formally applied but was discussed in an interview with applicant's representative on June 6, 1995. The patent teaches DTPA bifunctional chelating agents which may be complexed with the metal ions shown in Fig. 8 in columns 15-16. In the claims, hydroxybenzyl and methoxybenzyl substituents are recited as pending from the ethylene moiety, but these groups simply serve as linkers between the backbone and an amino acid. Although gadolinium metal is listed in the amended periodic table, paramagnetic gadolinium of Figure 8, paramagnetic gadolinium and its use in NMR diagnostics is not mentioned. Thus, the patent is not a statutory bar against the claims.

2. Claims 2-9, 11, 13, 14, 16, 18-26, 29, 30, 32 and 36-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 11 and 16 recite that  $Z^1$  and  $Z^2$  are a chain which can reduce to a phenyl group since at least one of  $q$  or  $l$  is one. It is not clear from this that the chain can reduce to a hydrogen atom which is also required by the proviso.

The Markush language in the independent claims is also unclear. Particularly, the language "one of the substituents  $Z^1$  and  $Z^2$ ." The *and* should be *or*. Similarly in "at least one of  $q$  and  $l$  is 1," the *and* should be *or*.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claim 16 is rejected under 35 U.S.C. 102(e) as being anticipated by Deutsch et al. (U.S. Pat. No. 5,482,700).

Deutsch et al. disclose a method of NMR diagnostics. Examples 10 and 12 describe the preparation of compounds of applicant's formula in claim 16.

5. Claim 16 is rejected under 35 U.S.C. 102(e) as being anticipated by Berg et al. (U.S. Pat. No. 5,198,208).

Berg et al. disclose DTPA derivatives used in diagnostic medicine. The examples teach such compounds wherein R<sup>1</sup> is hydroxymethyl or hydroxyethyl. These read on applicant's claims where k or r is 1 and R is an alkyl group.

6. Claims 2-9, 11, 13, 14, 18-26, 29, 30, 32 and 36-40 would be allowed if amended to overcome the rejection under 112, second paragraph.

Deutsch et al. (U.S. Pat. No. 5,482,700) disclose a method of NMR diagnostics wherein a Gd complex of a DTPA derivative is administered. See column 3, lines 12-23. The substituents R1 and R2 may be either a H or an alkylene group substituted with a phenyleneoxy. Exemplified species in columns 3-4 for R1 or R2 include substituents specifically excluded from claim 11 in the provisos. Thus, the patent is not a statutory bar. Based on Dr. Schumann-Giampieri's declaration of unexpected results for adjacent homologs, it would not have been obvious to modify the phenyleneoxy substituents of the Deutsch et al. compounds. Furthermore, Deutsch et al. disclose such substituents for the further attachment of macromolecules. To a person of ordinary skill in the art, it would not have been obvious to

exclude the macromolecules from the conjugates in performing NMR analysis or to pick applicant's species from the numerous substituents encompassed by the definition for R1 and R2.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gries et al. (U.S. Pat. No. 4,747,477) in combination with Gries et al. (U.S. Pat. No. 5,316,756) and Raduchel et al. (U.S. Pat. No. 5,399,340).

Gries '477 discloses DTPA complexes with paramagnetic metal ions for use in NMR imaging. Applicant's attention is directed to columns 1-2 where in Formula I, A is  $-\text{CH}_2-\text{CH}_2\text{ZCH}_2-\text{CH}_2)_m-$  and the Example in columns 11-12. Gries '477 do not teach that a phenyl ring is substituted on one of the mid-chain carbons. Gries '756 teaches NMR imaging using Gd chelates of DTPA analogs of Formula I. This reference teaches that R2 and R3 may be H, alkyl, phenyl or benzyl groups. Similarly, Raduchel discloses the use of Gd complexes of DTPA analogs for NMR where the mid-chain carbon atoms may be H, alkyl, phenyl or benzyl. Examples 14 and 15 demonstrate the attachment of a benzyl group in the R1 position. To a person of ordinary skill in the art, it would have been *prima facie* obvious to combine the teachings of all three commonly owned references to arrive at the instantly claimed methods since each explicitly teaches Gd-DTPA complexes for NMR imaging. Furthermore, as evidenced by Gries '756 and Raduchel, the substitution of phenyl and benzyl groups on mid-chain carbons of DTPA complexing agents is well known in the art. A person of ordinary skill in the art would therefore have been motivated to substitute a phenyl ring on a mid-chain carbon of a DTPA complex for use in a method of NMR analysis.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lara Chapman whose telephone number is (703) 308-0450. The examiner can normally be reached on Mondays through Thursdays and alternate Fridays from 7:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Kight, can be reached on (703) 308-0204. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.



JOHN KIGHT  
SUPERVISORY PATENT EXAMINER  
GROUP 1200



L. Chapman

September 12, 1996